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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,911	04/17/2001	Gyula Hadlaczky	24601-4021	7763

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/836,911	Applicant(s) HADLACZKY ET AL.	
	Examiner Ram R. Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,11,12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 23-60 are pending in the instant application.

Priority

It is noted that applicants have listed several applications, which they claim priority to and the filing dates for which date back to 1992. However, it is not clear as to when the claimed invention was first disclosed in the invention and therefore, the effective filing date for the claimed invention is assigned 4-10-1997,the filing date for application 08/835682, to which instant application (09/836,911) claims priority as a continuation.

2. Drawings are objected to for reasons shown on the Draftperson's Review PTO 948.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 23-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the

claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claimed invention encompasses producing transgenic animal by transferring introducing an artificial chromosome (broadly) or a satellite artificial chromosome in any cell and transferring the nucleus of the cell into any enucleated recipient cell and transferring the recipient cell into any maternal host animal. Dependent claims recite conditions, which the donor or recipients cells are produced in or are treated to. However, the specification as filed is not enabling for the claimed invention because the state of the art of producing transgenic animals from any donor cell into any recipient cell and for transfer of artificial chromosomes in a cell that could serve as donor cell was not predictable and an artisan of skill would have required extensive experimentation to practice the claimed invention and such experimentation would have been undue since the experimentation was not routine, and the state of the art was unpredictable and the specification did not teach how to address the limitations and unpredictable nature of the invention, as discussed below.

First, the only teaching in the specification about nuclear transfer method for producing a transgenic animal is on page 52, lines 22-32 continued in lines 1-7 on page 53 and the description recites Wilmut et al 1997, a nature article and two world documents which are applicants' there own and which have been issued as US patents 6,025,155 and 6,077,697. It is emphasized that these two patents by the applicants do not provide any guidance as to how to produce transgenic animals

by nucleus transfer. As for Wilmut et al 1997, the article of Wilmut et al does not provide enabling disclosure because this method has not been reproducible in other laboratories (see Wolf et al. Journal of Biotechnology 65:99-110, 1998, page 101, first full paragraph in the right column). It is emphasized that there are several factors that influence embryo cloning by nuclear transfer, such as the state and development and cell cycle of donor cells, the choice of the recipient cell, the methods of activation of the oocytes, cell cycle coordination between donor cell and the recipient cytoplast and the method for fusion between nuclear donor and recipient cytoplast (see the entire article by Wolf et al). The specification does not provide any specific teachings as regards any of these parameters. It should be noted that while there have been reports of animal cloning using nuclear transfer, there is no one protocol that can be used routinely for animal cloning using nuclear transfer and particularly, there was no routine method was available. The method of Wilmut has been questioned and even if it was not, it was a specific case which could not applied to any animal. Therefore, neither the specification nor the references cited in the specification provide guidance how to practice the claimed method.

In addition to the lack of a routine method of nuclear transfer and animal cloning, there are several limitations. For example, species-specific differences are major hurdle in animal cloning by nuclear transfer. For example, Stice et al (Therigeneology 49:129-138, 1998) reported that till 1998 there was only one successful example of nuclear transfer pig where the nucleus was derived from a four-cell state donor blastomere (see last two paragraphs on page 130). The authors suggested that the timing of the embryonic genome activation could be responsible for species-specific differences in cloning efficiency. Stice et al further noted that method used for cloning sheep where the donor cell was in G0 could not be used in other animal species (see the last paragraph on page 131). This clearly indicates that method used in one animal or species could not be used in anther animal or species. The specification does not provide any guidance as to how the claimed method will be practiced in the animal species as recited, for example in claim 30. It is noted that instantly claimed invention recite every possible method

of DNA introduction in a donor cell (direct uptake, calcium phosphate precipitation etc.) and every possible cell type as donor-such as embryo as a source wherein the embryo is developed in vitro or in vivo or fetus as a source or any enucleated cell, however, the specification does not provide guidance as to how the method will be carried out using these cells as donors or as recipients. It is noted that the only description for the claimed methods is present in the claims and there is no description as to how all these claimed methods will be practiced.

Yanagimachi (Molecular and Cellular Endocrinology 187:241-248, 2002) in their review of the state of the animal cloning noted:

"Perhaps, there is no single protocol for cloning that works for all mammalian species, because, the characteristics of oocytes and donor cells are different from species to species. A protocol that is the best for a given species may not be suitable for other species. Technical details must be worked out for each species. "

It is noted that applicants have not provided any protocol for producing any transgenic animal by nuclear transfer method.

Oback and Wells (Cloning and Stem Cells 4:169-174, 2002) in their review of the state of the art of donor cell selection for nuclear cloning noted:
"Cloning however is a multi-step procedure and exact contribution of the nuclear donor to overall cloning success must be determined in comparative studies. This requires strict standardization of isolation, purification, and culture protocols, and application of stringent identification criteria in order to obtain a homogenous donor cell population. In all these respects, the standards in the cloning field are currently poor."

This again demonstrates that donor cell selection and preparation was not routine even in 2002 and required extensive experimentation.

Kuhholzer and Prather (The Society for Experimental Biology and Medicine 224:240-245, 2000) reviewed the state of the art of nuclear transfer in 2000 and noted,

"The techniques of NT have improved dramatically over the last 5 years, but still are far from using a perfect protocol.....These abnormalities seem to be an indication of incomplete reprogramming, and much effort will be put into

investigating this issue. One important step to enlighten the exact mechanisms of reprogramming is analyzing differences in gene-expression patterns of early embryos derived ex vivo, in vitro and by NT using different sources of donor cells as well as species-specific differences."

The statement by Kuhholzer et al very clearly demonstrates the state of the art of producing transgenic animal by nuclear transfer and the specification does not provide any guidance to address any of the issues discussed above and therefore an artisan of skill would have not been able to practice the claimed method without extensive experimentation which would have been undue due to the lack of direction in the art and in the specification and because such experimentation would not have been routine at the time of the invention.

Co et al (Chromosome Research 8:183-191, 2000) reported generation of transgenic mice and germline transmission of a murine SATAC introduced into embryos by pronuclear microinjection, the article does not provide any guidance regarding nuclear transfer. While this article teaches that SATAC are stable, the introduction of a SATAC containing a heterologous sequence in a donor cell and use of the donor cell in producing a transgenic mammal will be unpredictable in view of the discussion above and the unpredictable art of transgenesis based on the discussion above.

In conclusion, the specification as filed is not enabling for the claimed invention because the state of the art of producing transgenic animals from any donor cell into any recipient cell and for transfer of artificial chromosomes in a cell that could serve as donor cell was not predictable and an artisan of skill would have required extensive experimentation to practice the claimed invention and such experimentation would have been undue since the experimentation was not routine, and the state of the art was unpredictable and the specification did not teach how to address the limitations and unpredictable nature of the invention.

5. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Tiffiany N. Tabb whose telephone number is (703) 605-1238.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER